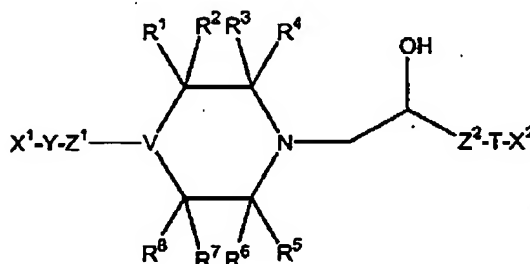


Response to July 6, 2005, Office Action  
 Atty Dkt No. 01-0159-CIP-2  
 Application No. 10/759,562

# APPENDIX A

## CLEAN COPY OF CLAIMS AS AMENDED HEREIN

1. A compound of the formula:



Formula I

wherein:

$R^1, R^2, R^3, R^4, R^5, R^6, R^7$ , and  $R^8$  are hydrogen, lower alkyl, or  $-C(O)R$ ; in which  $R$  is  $-OR^9$  or  $NR^9R^{10}$ , where  $R^9$  and  $R^{10}$  are hydrogen or lower alkyl; or  $R^1$  and  $R^2, R^3$  and  $R^4, R^5$  and  $R^6, R^7$  and  $R^8$ , when taken together with the carbon to which they are attached, represent carbonyl; or  $R^1$  and  $R^5$ , or  $R^1$  and  $R^7$ , or  $R^3$  and  $R^5$ , or  $R^3$  and  $R^7$ , when taken together form a bridging group  $-(CR^{12}R^{13})_n-$ , in which  $n$  is 1, 2 or 3, and  $R^{12}$  and  $R^{13}$  are independently hydrogen or lower alkyl;

with the provisos that

- i. the maximum number of carbonyl groups is 2;
- ii. the maximum number of  $-C(O)NR^9R^{10}$  groups is 1; and
- iii. the maximum number of bridging groups is 1;

$T$  is oxygen or sulfur;

$V$  is  $-N<$ ;

$X^1$  is optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

$X^2$  is optionally substituted aryl or optionally substituted heteroaryl;

Response to July 6, 2005, Office Action  
Atty Dkt No. 01-0159-CIP-2  
Application No. 10/759,562

Y is optionally substituted monocyclic heteroarylenyl; and

Z<sup>1</sup> and Z<sup>2</sup> are independently optionally substituted alkylene of 1-4 carbon atoms.

3. The compound of claim 1, wherein T is oxygen.
4. The compound of claim 3, wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are independently chosen from hydrogen and methyl.
5. The compound of claim 4, wherein X<sup>1</sup> is optionally substituted aryl or optionally substituted heteroaryl.
6. The compound of claim 5, wherein X<sup>2</sup> is optionally substituted phenyl or optionally substituted bicyclic heteroaryl.
7. The compound of claim 6, wherein X<sup>2</sup> is 2-methylbenzothiazol-5-yl, 2-cyclohexylbenzothiazol-5-yl, 2-phenylbenzothiazol-5-yl, or 2-phenylbenzoxazol-5-yl.
8. The compound of claim 7, wherein Z<sup>1</sup> and Z<sup>2</sup> are both methylene.
9. The compound of claim 8, wherein Y is a diradical derived from pyrazole, benzoxazole, isoxazole, 1,3-oxazole, 1,3-thiazole, 1,2,4-oxadiazole, or 1,3,4-oxadiazole.
10. The compound of claim 9, wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are all hydrogen.
11. The compound of claim 9, wherein one of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> is methyl and the remainder are hydrogen.
12. The compound of claim 9, wherein X<sup>1</sup> is phenyl optionally substituted by lower alkyl, lower alkoxy, halogen, phenyl, or trifluoromethyl.

Response to July 6, 2005, Office Action  
Atty Dkt No. 01-0159-CIP-2  
Application No. 10/759,562

13. The compound of claim 9, wherein Y is an isoxazole diradical.

14. (The compound of claim 13, wherein the compound is selected from the group consisting of:

(2R)-1-((2S)-4-{{5-(4-chlorophenyl)isoxazol-3-yl}methyl}-2-methylpiperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;

(2R)-3-(4-{{5-(4-chlorophenyl)isoxazol-3-yl}methyl}piperazinyl)-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol;

(2R)-3-[(2S)-2-methyl-4-{{5-[2-chlorophenyl]isoxazol-3-yl}methyl}piperazinyl]-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol;

(2R)-3-{{(3S)-3-methyl-4-{{5-(3,4-dichlorophenyl)isoxazol-3-yl}methyl}piperazinyl}-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol};

(2R)-3-{{(3S)-3-methyl-4-{{5-(2-chlorophenyl)isoxazol-3-yl}methyl}piperazinyl}-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol};

(2R)-3-{{(3S)-3-methyl-4-{{5-(4-chlorophenyl)isoxazol-3-yl}methyl}piperazinyl}-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol};

(2S)-3-((2S)-4-{{5-(3,4-dichlorophenyl)isoxazol-3-yl}methyl}-2-methylpiperazinyl)-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol;

(2R)-3-{{(2S)-2-methyl-4-{{5-phenylisoxazol-3-yl}methyl}piperazinyl}-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol};

(2R)-3-{{(3S)-3-methyl-4-{{5-(4-trifluoromethylphenyl)isoxazol-3-yl}methyl}piperazinyl}-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol};

(2R)-1-(2-methylbenzothiazol-5-yloxy)-3-[4-{{5-[4-(trifluoromethyl)phenyl]isoxazol-3-yl}methyl}piperazinyl]propan-2-ol;

(2R)-3-{{(3S)-3-methyl-4-{{5-(4-phenylphenyl)isoxazol-3-yl}methyl}piperazinyl}-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol};

(2R)-3-{{(3S)-3-methyl-4-{{3-(4-methoxyphenyl)isoxazol-5-yl}methyl}piperazinyl}-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol};

(2R)-3-[(2S)-2-methyl-4-{{5-[4-chlorophenyl]isoxazol-3-yl}methyl}piperazinyl]-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol;

(2R)-3-[(2S)-2-methyl-4-{{5-[2-chlorophenyl]isoxazol-3-yl}methyl}piperazinyl]-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol;

Response to July 6, 2005, Office Action  
Amended Dkt No. 01-0159-CIP-2  
Application No. 10/759,562

(2R)-3-((2S)-4-([5-(3,4-dichlorophenyl)isoxazol-3-yl]methyl)-2-methylpiperazinyl)-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol;

(2R)-3-((2S)-2-methyl-4-[(3-(4-methoxyphenyl)isoxazol-5-yl)methyl]piperazinyl)-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol;

(2R)-3-((2S)-2-methyl-4-[(3-phenylisoxazol-5-yl)methyl]piperazinyl)-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol; and

(2R)-3-((2R)-2-methyl-4-[(3-(4-methoxyphenyl)isoxazol-5-yl)methyl]piperazinyl)-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

15. The compound of claim 9, wherein Y is a 1,3-thiazole diradical.

16. The compound of claim 15, wherein the compound is selected from the group consisting of:

(2R)-1-(4-([2-(4-chlorophenyl)(1,3-thiazol-4-yl)]methyl)piperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;

(2R)-1-((3S)-4-([2-(4-chlorophenyl)(1,3-thiazol-4-yl)]methyl)-3-methylpiperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;

(2R)-3-(2-methylbenzothiazol-5-yloxy)-1-{4-[(2-phenyl(1,3-thiazol-4-yl))methyl]piperazinyl}propan-2-ol;

(2R)-1-((3S)-3-methyl-4-[(2-phenyl(1,3-thiazol-4-yl))methyl]piperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol; and

(2R)-1-[(3S)-3-methyl-4-({2-[4-(trifluoromethyl)phenyl](1,3-thiazol-4-yl))methyl]piperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

17. The compound of claim 9, wherein Y is a 1,2,4-oxadiazole diradical.

18. The compound of claim 17, wherein the compound is selected from the group consisting of:

(2R)-3-[4-({3-[4-(tert-butyl)phenyl](1,2,4-oxadiazol-5-yl)}methyl)piperazinyl]-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol;

(2R)-3-((2S)-2-methyl-4-[(3-(2-thienyl)(1,2,4-oxadiazol-5-yl))methyl]piperazinyl)-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol;

Response to July 6, 2005, Office Action  
Atty Dkt No. 01-0159-CIP-2  
Application No. 10/759,562

- (2R)-1-(4-{[3-(2,4-dichlorophenyl)(1,2,4-oxadiazol-5-yl)]methyl}piperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-1-((2S)-4-{[3-(2,4-dichlorophenyl)(1,2,4-oxadiazol-5-yl)]methyl}-2-methylpiperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-1-(4-{[3-(2-chlorophenyl)(1,2,4-oxadiazol-5-yl)]methyl}piperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-1-(4-{[3-(2-fluorophenyl)(1,2,4-oxadiazol-5-yl)]methyl}piperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-3-(2-methylbenzothiazol-5-yloxy)-1-(4-{[3-(2-methylphenyl)(1,2,4-oxadiazol-5-yl)]methyl}piperazinyl)propan-2-ol;
- (2R)-1-[(2S)-2-methyl-4-({5-[3-(trifluoromethyl)phenyl](1,2,4-oxadiazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-1-((3S)-4-{[5-(2,4-dichlorophenyl)(1,2,4-oxadiazol-3-yl)]methyl}-3-methylpiperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-3-(2-methylbenzothiazol-5-yloxy)-1-[4-({5-[3-(trifluoromethyl)phenyl](1,2,4-oxadiazol-3-yl)}methyl)piperazinyl]propan-2-ol;
- (2R)-3-(2-methylbenzothiazol-5-yloxy)-1-(4-{[5-(2-methylphenyl)(1,2,4-oxadiazol-3-yl)]methyl}piperazinyl)propan-2-ol;
- (2R)-1-(4-{[5-(2-chlorophenyl)(1,2,4-oxadiazol-3-yl)]methyl}piperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-1-(4-{[5-(2-fluorophenyl)(1,2,4-oxadiazol-3-yl)]methyl}piperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-3-{4-[3-(4-t-butylphenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazin-1-yl}-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-3-{4-[5-(4-(trifluoromethyl)phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazin-1-yl}-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-1-(2-methylbenzothiazol-5-yloxy)-3-[4-({5-[4-(trifluoromethyl)phenyl](1,2,4-oxadiazol-3-yl)}methyl)piperazinyl]propan-2-ol;
- (2R)-1-[(3S)-3-methyl-4-({5-[4-(trifluoromethyl)phenyl](1,2,4-oxadiazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol; and
- (2R)-3-[(2S)-2-methyl-4-({5-[4-(trifluoromethyl)phenyl](1,2,4-oxadiazol-3-yl)}methyl)piperazinyl]-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

Response to July 6, 2005, Office Action  
Atty Dkt No. 01-0159-CIP-2  
Application No. 10/759,562

19. The compound of claim 9, wherein Y is a benzoxazole diradical.
20. The compound of claim 19, wherein the compound is selected from the group consisting of:
- (2R)-3-(2-methylbenzothiazol-5-yloxy)-1-{4-[(5-phenylbenzoxazol-2-yl)methyl]piperazinyl}propan-2-ol; and
- (2R)-3-[(2S)-2-methyl-4-[(5-phenylbenzoxazol-2-yl)methyl]piperazinyl]-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol.
21. The compound of claim 9, wherein Y is a 1,3,4-oxadiazole diradical.
22. The compound of claim 21, wherein the compound is selected from the group consisting of:
- (2R)-1-[(2S)-2-methyl-4-{[5-(4-methylphenyl)(1,3,4-oxadiazol-2-yl)]methyl}piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-1-[(2S)-4-{[5-(4-chlorophenyl)(1,3,4-oxadiazol-2-yl)]methyl}-2-methylpiperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-1-(4-{[5-(4-chlorophenyl)(1,3,4-oxadiazol-2-yl)]methyl}piperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-3-(2-methylbenzothiazol-5-yloxy)-1-(4-{[5-(4-methylphenyl)(1,3,4-oxadiazol-2-yl)]methyl}piperazinyl)propan-2-ol;
- (2R)-3-(2-methylbenzothiazol-5-yloxy)-1-[4-({5-[4-(trifluoromethyl)phenyl](1,3,4-oxadiazol-2-yl)]methyl}piperazinyl)]propan-2-ol;
- (2R)-3-(2-methylbenzothiazol-5-yloxy)-1-[4-({5-[3-(trifluoromethyl)phenyl](1,3,4-oxadiazol-2-yl)]methyl}piperazinyl)]propan-2-ol;
- (2R)-3-(2-methylbenzothiazol-5-yloxy)-1-(4-{[5-(4-phenylphenyl)(1,3,4-oxadiazol-2-yl)]methyl}piperazinyl)propan-2-ol;
- (2R)-1-[4-({5-[4-(tert-butyl)phenyl](1,3,4-oxadiazol-2-yl)]methyl}piperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-3-(2-methylbenzothiazol-5-yloxy)-1-{4-[(5-(2-naphthyl)(1,3,4-oxadiazol-2-yl))methyl]piperazinyl}propan-2-ol;

Response to July 6, 2005, Office Action  
Atty Dkt No. 01-0159-CIP-2  
Application No. 10/759,562

- (2R)-1-[4-({5-[4-(dimethylamino)phenyl](1,3,4-oxadiazol-2-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-1-(4-{{5-(2-chlorophenyl)(1,3,4-oxadiazol-2-yl)}methyl}piperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-1-(4-{{5-(4-methoxyphenyl)(1,3,4-oxadiazol-2-yl)}methyl}piperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-3-(2-methylbenzothiazol-5-yloxy)-1-{4-[(5-phenyl(1,3,4-oxadiazol-2-yl))methyl]piperazinyl}propan-2-ol;
- (2R)-1-{{(2S)-2-methyl-4-[(5-phenyl(1,3,4-oxadiazol-2-yl))methyl]piperazinyl}-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol};
- (2R)-1-[(2S)-2-methyl-4-({5-[3-(trifluoromethyl)phenyl](1,3,4-oxadiazol-2-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-1-((2S)-2-methyl-4-{{5-[4-phenylphenyl](1,3,4-oxadiazol-2-yl)}methyl}piperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-1-[(2S)-4-({5-[4-(tert-butyl)phenyl](1,3,4-oxadiazol-2-yl)}methyl)-2-methylpiperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-1-{{(2S)-2-methyl-4-[(5-(2-naphthyl)(1,3,4-oxadiazol-2-yl))methyl]piperazinyl}-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol};
- (2R)-1-[(2S)-4-({5-[4-(dimethylamino)phenyl](1,3,4-oxadiazol-2-yl)}methyl)-2-methylpiperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-3-((2S)-4-{{5-(2-chlorophenyl)(1,3,4-oxadiazol-2-yl)}methyl}-2-methylpiperazinyl)-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol;
- (2R)-3-((2S)-4-{{5-(4-methoxyphenyl)(1,3,4-oxadiazol-2-yl)}methyl}-2-methylpiperazinyl)-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol; and
- (2R)-1-[(2S)-2-methyl-4-({5-[4-(trifluoromethyl)phenyl](1,3,4-oxadiazol-2-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

23. The compound of claim 9, wherein Y is a 1,3-oxazole diradical.

24. The compound of claim 23, wherein the compound is selected from the group consisting of (2R)-3-[(2S)-2-methyl-4-({2-[4-(trifluoromethyl)phenyl](1,3-oxazol-5-yl)}methyl)piperazinyl]-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol and (2R)-1-(2-

Response to July 6, 2005, Office Action  
Atty Dkt No. 01-0159-CIP-2  
Application No. 10/759,562

methylbenzothiazol-5-yloxy)-3-[4-( {2-[4-(trifluoromethyl)phenyl](1,3-oxazol-4-yl))methyl)piperazinyl]propan-2-ol.

25 A method of treating a disease state chosen from diabetes, damage to skeletal muscles resulting from trauma or shock and a cardiovascular disease in a mammal by administration of a therapeutically effective dose of a compound of claim 1.

26. The method of claim 25, wherein the cardiovascular disease is atrial arrhythmia, intermittent claudication, ventricular arrhythmia, Prinzmetal's (variant) angina, stable angina, unstable angina, congestive heart disease, or myocardial infarction.

27. The method of claim 25, wherein the disease state is diabetes.

28. A pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and a therapeutically effective amount of a compound of claim 1.

29 A method of preserving donor tissue and organs used in transplants, comprising administering to a mammal in need thereof a therapeutically effective dose of a compound of claim 1.